REMARKS

Claim 1-5, 9 and 10, as amended, remain herein. New claims 11-25 are added.

Claim 1 previously recited narrower ranges within broad ranges. Pursuant to the helpful suggestions from the Office Action, the narrow ranges recited in claim 1 have been removed and are now recited in new claims 11 through 25. Claim 1 has also been amended to recite a method for the treatment of urinary incontinence. Likewise, claims 2 and 5 now recite a method.

Claims 1 through 5, 9 and 10 were rejected under § 103 over Merck Index #4852 (Merck) and Morikawa et al.

Merck teaches indomethacin as useful for treating inflammation. Morikawa is relied upon to teach indomethacin with various pharmaceutical carriers and the administration of a proper dosage. The Office Action concedes that these primary references fail to specifically recite those medicaments set forth in Applicants' presently claimed invention.

One aspect of Applicants' presently claimed invention is the use of the Nitro-oxy derivative of indomethacin or NOI for the treatment of urinary incontinence. On page 51 of applicants specification in Table 1, one sees a comparison between the efficacy of indomethacin (1D) compared with the nitro derivative of Example 3. Applicants' nitro derivative inhibits contraction by 48.1%, in contrast to the efficacy of indomethacin at 38.5%. The presently claimed invention is nearly 25% more efficient than the cited prior art. Table 2 at page 52 and Table 3 at page 54, Table 4 at page 55 and Table 5 at page 57 all show the same dramatic effects. Applicant's presently claimed invention, as

demonstrated by comparison testing, provides dramatic improvement over the cited prior art.

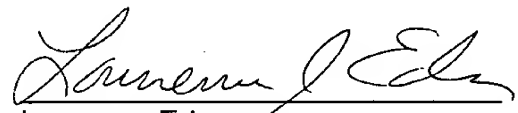
There is no teaching in either Merck Index #4852 or Morikawa et al. suggesting applicants' presently claimed invention, nor is there any teaching which would suggest effectively combining those two references to suggest the presently claimed invention. Therefore, Applicants respectfully requests that this rejection be withdrawn, and claims 1 through 5 and 9 through 10 be allowed.

For the foregoing reasons, the claims now particularly point out and distinctly claim what applicants regard as their invention in a manner patentably distinguished over all grounds of rejection cited in the Office Action. Accordingly, allowance of all claims 1-5 and 9-25 is respectfully requested.

Should the Examiner deem that any further action by the applicants would be desirable for placing this application in even better condition for issue, the Examiner is requested to telephone applicants' undersigned representative at the number listed below.

Please charge any fee deficiency or credit any overpayment to Deposit Account No. 01-2300, referencing Attorney Docket No. 108907-09002.

Respectfully submitted,



Laurence Edson
Registration No. 44,666

Customer No. 004372
ARENT FOX KINTNER PLOTKIN & KAHN, PLLC
1050 Connecticut Avenue, N.W.
Suite 600
Washington, D.C. 20036-5339
Tel: (202) 857-6000
Fax: (202) 638-4810

MARKED-UP CLAIMS FOR 9/147,770

1. (Twice Amended) [Use of the following groups of compounds, or their compositions, for the preparation of medicaments for the] A method for treatment of urinary incontinence by administering compounds, having the [general] formula:

$$A\text{-}X_1\text{-}NO_2$$

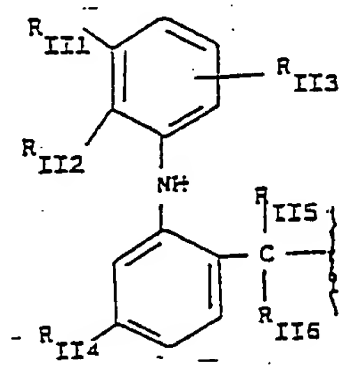
or their salts, where:

A = $R(COX)_t$ [where] wherein t is an integer 0 or 1;

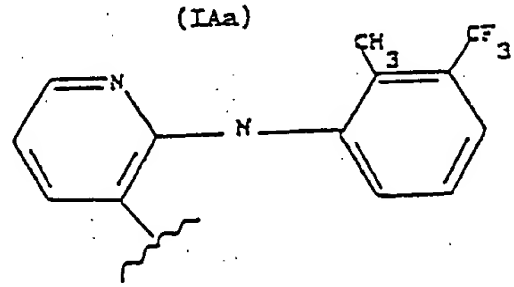
X = O, NH, NR_{1C} [where] wherein R_{1C} is a linear or branched alkyl having from 1 to 10 C atoms;

R is chosen from the following groups:

[*] Group I A), where t = 1,



(IAa)



(IAb)

where:

R_{II5} is H, a linear C_1-C_3 alkyl, or [whenever possible] a branched C_1-C_3 alkyl;

R_{II6} has the same structure [meanings] as R_{II5}, [or when R_{II5} is H it can be benzyl;]

R_{II1}, R_{II2} and R_{II3} are each [equal or different one from the other and are] hydrogen[s], linear C_1-C_6 alkyl [or whenever possible] branched C_1-C_6 alkyl, [or] C_1-C_6 alkoxy, [or] Cl, F, or Br;

R_{II4} has the same structure as [is] R_{II1} or is bromine;

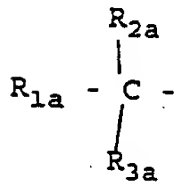
[preferred are the compounds where R_{II1}, R_{II2} and R_{II4} are H, and R_{II3} is in the ortho position to NH; R_{II5} and R_{II6} are H, X is equal to O, and X_1 is $(CH_2\text{-}CH_2\text{-}O)_2$;

(I Ab) is the residue of 2-((2-methyl-3-(trifluoromethyl)phenyl)amino)-3-pyridinecarboxylic acid [and when -COOH is present it is known as flunixin].

[The compounds preferred are those where X = O;]

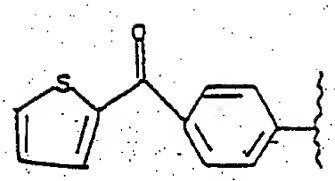
[*] Group II A) chosen from the following:

where, when t = 1, R is

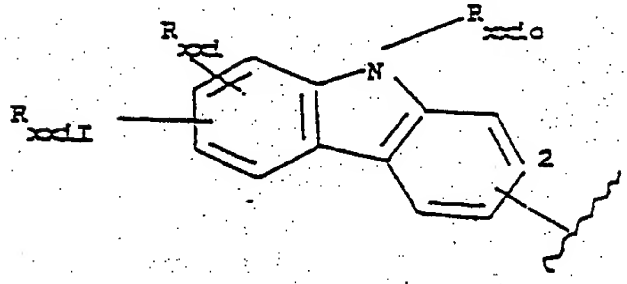


where R_{2a} and R_{3a} are H, a linear C_1-C_{12} alkyl, [or whenever possible] branched [substituted or non-substituted] C_1-C_{12} alkyl, or allyl, with the proviso that when one of the two is allyl the other is H; [preferably R_{2a} is H, alkyl has from 1 to 4 C atoms, R_{3a} is H];

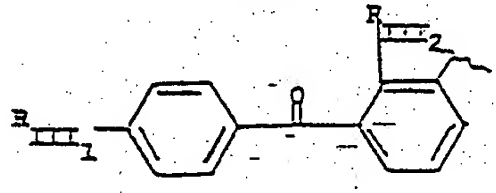
R_{1a} is chosen from the subgroup II Aa) consisting of



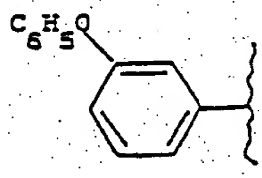
(II)



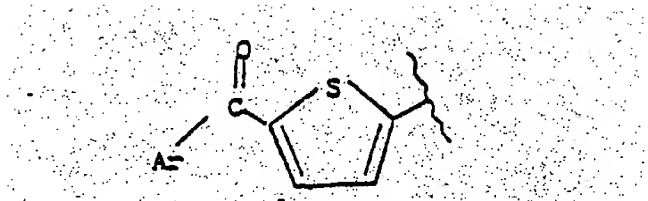
(XXI)



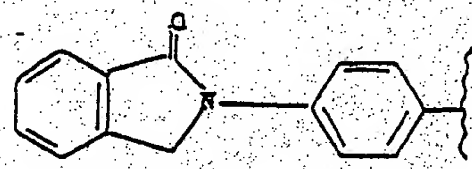
(IV)



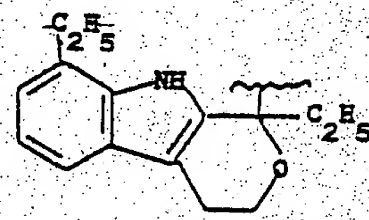
(VII)



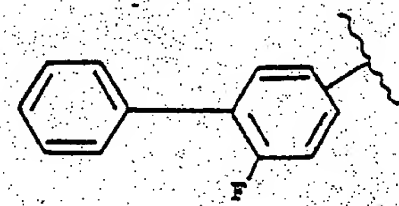
(XXXV)



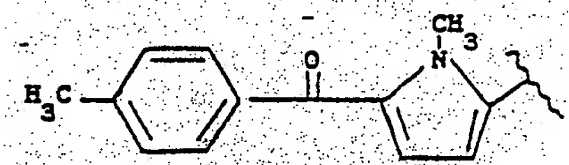
(VI)



(VIII)

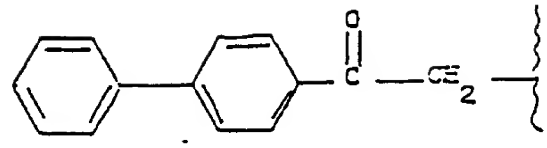


(IX)



(X)

, and



(III)

wherein [meanings are as follows]:

in the reside [compounds] of formula (IV), [residue of]:

R_{III1} is H[,] or SR_{III3} where R_{III3} contains from 1 to 4 [C] linear or [whenever possible] branched C atoms; and

R_{III2} is H[,] or hydroxy;

[preferred are the compounds where R_{III1} and R_{III2} are H, R_{3a} is H, and R_{2a} is methyl, X = O;]

[-] in the residue [compounds] of formula (XXI), [residue of carprofen]:

R_{xxio} is H; a linear alkyl having 1-6 carbon atoms, [or whenever possible] a branched alkyl having from 1 to 6 carbon atoms, a C_1-C_6 alkoxy-carbonyl bound to a C_1-C_6 carboxyalkyl, or a C_1-C_6 alkanoyl [optionally substituted with halogen, benzyl or halobenzyl, benzoyl or halobenzoyl];

R_{xxi} is H, halogen, hydroxy, CN, a C_1-C_6 alkyl, [optionally containing OH groups,] a C_1-C_6 alkyl; a perfluoroalkyl having a 1-3 C atoms, a C_1-C_6 carboxyalkyl [optionally containing OH groups], NO_2, sulphamoyl, dialkyl sulphamoyl with the alkyl having from 1 to 6 C atoms, or difluoroalkylsulphonyl with the alkyl having from 1 to 3 C atoms;

R_{xxii} is halogen, CN, a C_1-C_6 alkoxy, acetyl, acetamido, or benzyloxy, SR_{III3} [is as above defined], a perfluoroalkyl having from 1 to 3 C atoms, hydroxy, a carboxyalkyl having from 1 to 6 C atoms, hydroxy, a caroboxyalkyl having from 1 to 6 C atoms, NO_2, amino, mono- or dialkylamino having from 1 to 6 C atoms, sulphamoyl, a

dialkyl sulphamoyl having from 1 to 6 C atoms, [or] difluoroalkylsulphamoyl [defined]; or

R_{xxi} together with R_{xxi1} an alkylene dioxy having from 1 to 6 C atoms;

[preferred are the compounds where R_{xxio} is H, the connecting bridge is at position 2, R_{xxi} is H, R_{xxi1} is chlorine and is in the para position to nitrogen;

R_{3a} is H, R_{2a} is methyl and X is O;]

in the residue [compounds] of formula (XXXV), [residue of thiaprofenic acid]:

Ar is phenyl, hydroxyphenyl optionally mono- or polysubstituted with halogen, an alkanoyl or alkoxy having from 1 to 6 C atoms, a trialalkyl having from 1-6 C atoms, [preferably from 1-3 C atoms,] cyclopentyl o-hexyl o-heptyl, [heteroaryl, preferably] thienyl, furyl, [optionally] furyl containing OH, or pyridyl; [the preferred compounds of formula (XXXV) are those where Ar is phenyl, R_{3a} is H, R_{2a} is methyl and X is O; in the compounds of formula (II), residue of suprofen,

the preferred, where R_{3a} = H, R_{2a} = CH_3 and X = O;

in the compounds of formula (VI), of which the preferred, indoprofen, when R_{2a} is CH_3 and X = O;

- in the compounds of formula (VIII),

of which the preferred, etodolac, when R_{3a} = R_{2a} = H and X = O;

- in the compounds of formula (VII),

of which the preferred, fenoprofen, when R_{3a} = R_{2a} = H and X = O;

- in the compounds of formula (III),

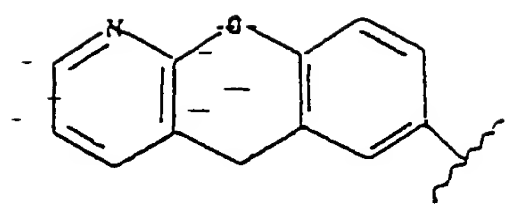
of which the preferred, fenbufen, when R_{3a} = R_{2a} = H and X = O;

- in the compounds of formula (X), residue of tolmetin, when R_{3a} = R_{2a} = H and X = O;

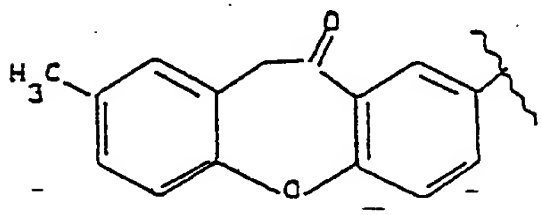
- in the compounds of formula (IX), residue of flurbiprofen, when R_{3a} = H, R_{2a} = CH_3 and X = O;]

subgroup II Ab)consisting of:

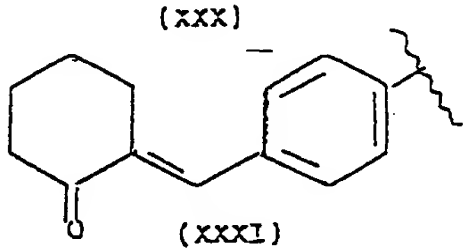
II Ab):



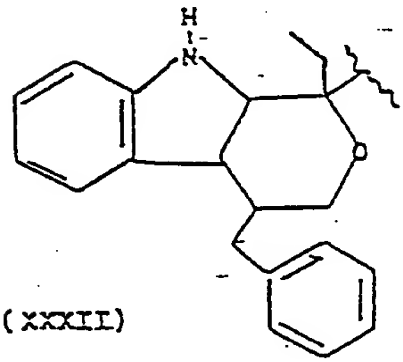
IIIa)



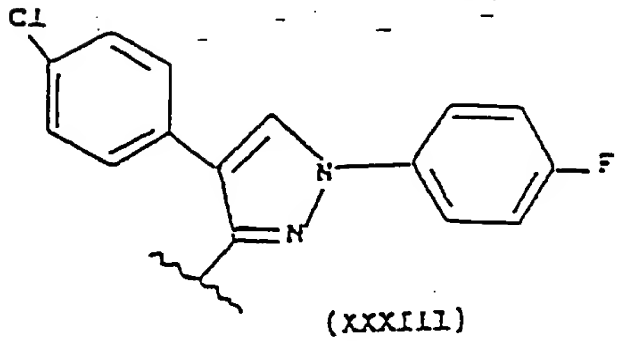
(XXX)



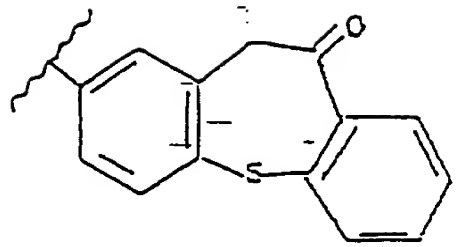
(XXXI)



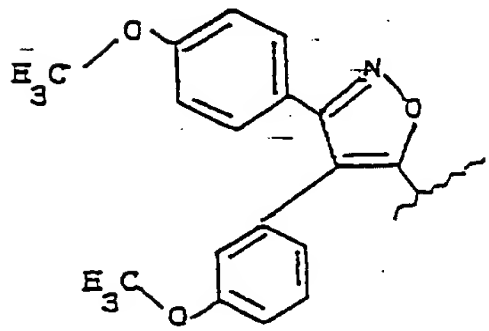
(XXXII)



(XXXIII)



(XXXVI)



(XXXVII)

wherein [the meanings are as follows]:

[-] when IIIa) contains -CH(CH_3)-COOH it is known as pranoprofen: α-methyl-5H-(1) benzopyran (2,3-b) pyridine-7-acetic acid; [preferred R_{2a} = H, R_{3a} = CH_3 and X = O;]

[-] when residue (XXX) contains -CH(CH_3) -COOH it is known as bermoprofen: dibenz (b,f) oxepin-2-acetic acid, [preferred is X = O, R_{2a} = H, R_{3a} = CH_3;]

[-] residue (XXXI) is known as CS-670: 2-(4-2(2-oxo-1-cyclohexylidenemethyl) phenyl) propionic acid, when the radical is -CH(CH_3) -COOH; [preferred R_{2a} = H, R_{3a} = CH_3 and X = O;]

[-] when residue (XXXIII) is saturated with -CH_2COOH it is known as pyrazolac: 4-(4-chlorophenyl)-1-(4-fluorophenyl) 3-pyrazolyl acid derivatives; [preferred $R_{2a} = R_{3a} = H$ and X = O;]

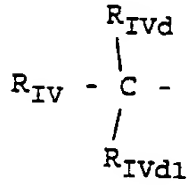
[- when residue (XXXVI) is saturated with -$CH(CH_3)$ -COO- it is known as zaltoprofen.

when the residue is saturated with a hydroxy or amine group or the acid salts, the compounds are known as dibenzothiepin derivatives.

Preferred $R_{2a} = H$, $R_{3a} = CH_3$ and X = O];

[-] when residue (XXXVII) is CH_2-COOH it derives from the known mofezolac: 3,4-di p-methoxyphenyl) isoxazol-5-acetic acid; [preferred are $R_{2a} = R_{3a} = H$, t = 1, X = O.]

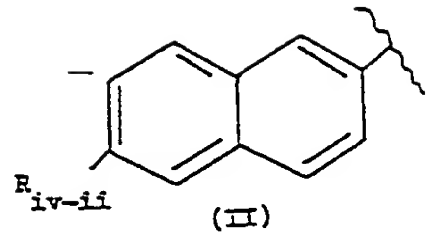
[*] Group IIIA), where t = 1,[.]



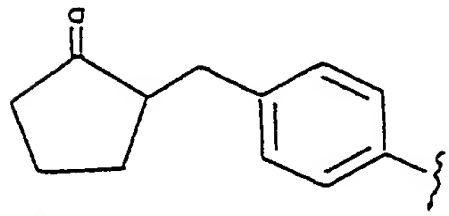
wherein:

at least one of R_{Ivd} and R_{Ivd1} [are] [at least one] is H and the other a linear or [whenever possible] branched C_1-C_6 alkyl, [preferably C_1-C_2,] or difluoroalkyl with the alkyl having from 1 to 6 C atoms, [preferred is C_1] or R_{Ivd} and R_{Ivd} jointly form a methylene group;

R_{IV} has the following structure [meaning]:

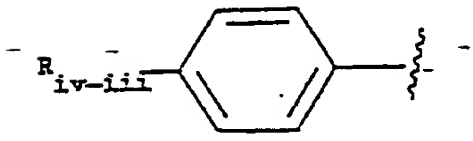


(II)



, or

(X)



(III)

where [the compounds of group IIIA) have the following meanings]:

[-]in the residue [compounds] of formula (II):

R_{IV-II} is selected from the group consisting of an alkyl having from 1 to 6 C atoms, a cycloalkyl having from 3 to 7 C atoms, an alkoxymethyl [alcoxymethyl] having from 1 to 7 C atoms, a trifluoroalkyl having from 1 to 3 C atoms, vinyl, ethynyl, halogen, an alkoxy having from 1 to 6 C atoms, a difluroalkoxy with the alkyl having from 1 to 7 C atoms, an alkoxymethyloxy having from 1 to 7 C atoms, an alkylthiomethyloxy with the alkyl having from 1 to 7 C atoms, an alkylmethylthio with the alkyl having from 1 to 7 C atoms, cyano, difluoromethylthio, a substituted phenyl-, [or] and phenylalkyl with the alkyl having from 1 to 8 C atoms;

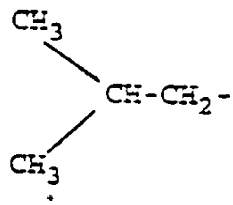
[preferably R_{IV-II} is CH_3O, R_{Ivd} is H and R_{Ivd1} is CH_3, and is known as the residue of naproxen;

X = NH and X_1 is equal to $(CH_2)_4$ or $(CH_2CH_2O)_2$; [also preferred is the same compound where X is equal to O;

- in the preferred compounds of formula (X), for which the residue of loxoprofen has been shown, R_{Ivd} is H and R_{Ivd1} is CH_3, X = NH or O and X_1 is equal to $(CH_2)_4$ or $(CH_2CH_2O)_2$;
- in the compounds of formula (III):]

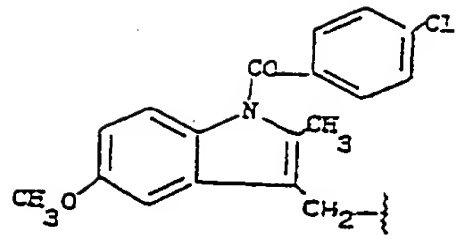
R_{IV-III} is a C_2-C_5 alkyl, [even branched when possible], a C_2 and C_3 alkyloxy, allyloxy, phenoxy, phenylthio, a cycloalkyl having from 5 to 7 C atoms, optionally substituted at position 1 by a C_1-C_2 alkyl;

[preferred is the compound where R_{IV-III} is



and R_{Ivd} = H, R_{Ivd1} is CH_3, a compound known as the residue of ibuprofen; X = NH and X_1 is equal to $(CH_2)_4$ or $(CH_2CH_2O)_2$; also preferred is the same compound where X = O;]

[*]Group IV A)



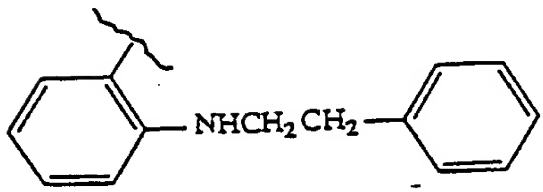
(IV)

where A = RCOO, t = 1,

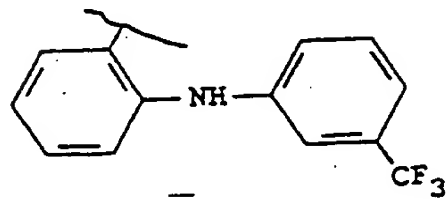
[of which the residue of the known indomethacin has been shown.

*]Group V A) chosen from the following:

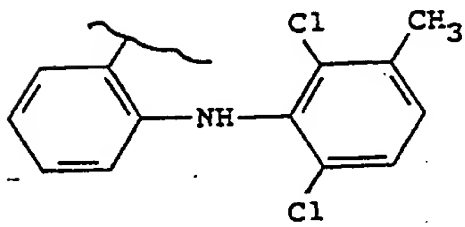
[-] subgroup V Aa) residues [fenamates] chosen from the following, where t = 1



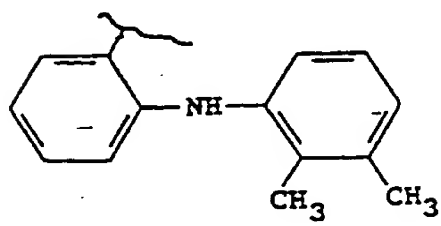
(V Aa1)



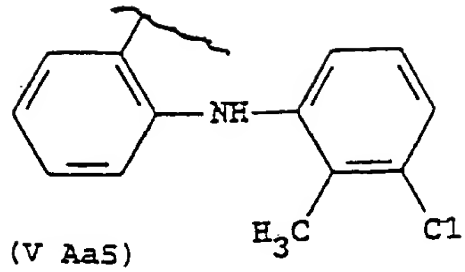
(V Aa2)



(V Aa3)

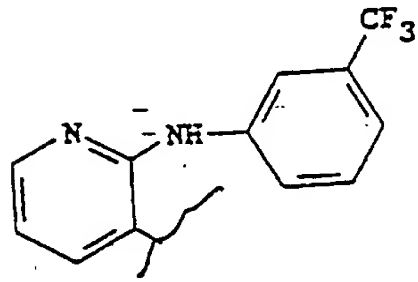


(V Aa4)



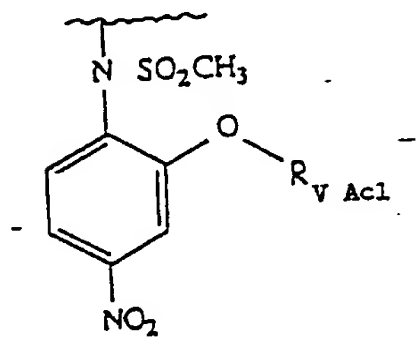
(V Aa5)

subgroup - V Ab), residue [derivatives of niflumic acid], where t = 1:

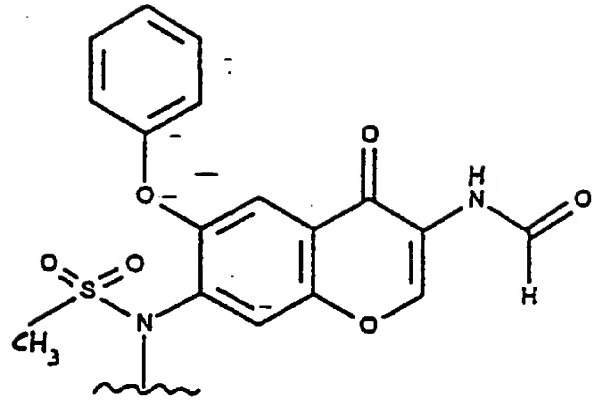


(V Ab1)

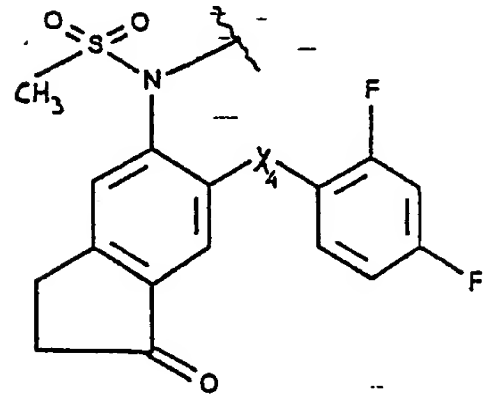
subgroup - V Ac), residue [COX_2 inhibitors], where t = 0 and R is as follows:



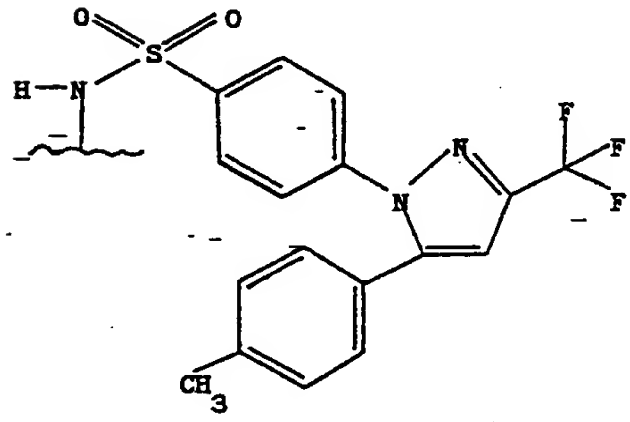
(V Ac1)



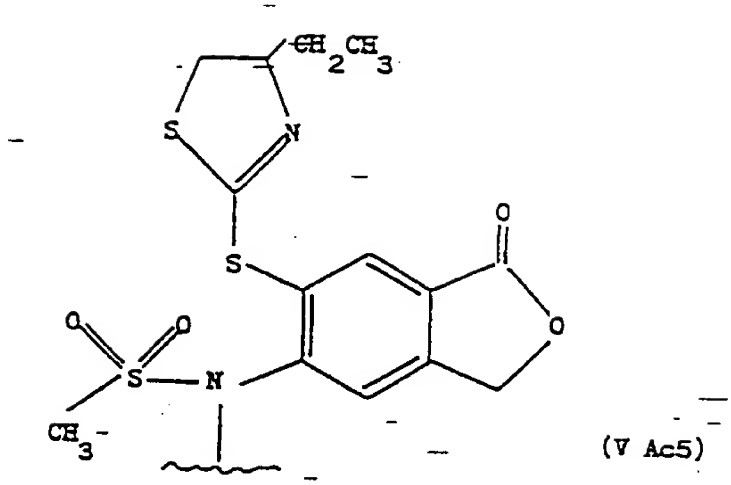
(V Ac2)



(V Ac3)

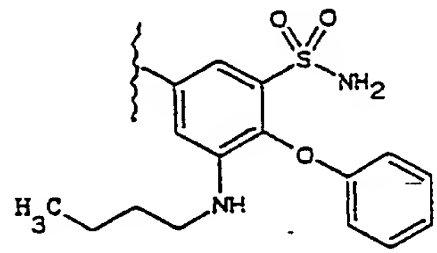


(V Ac4)

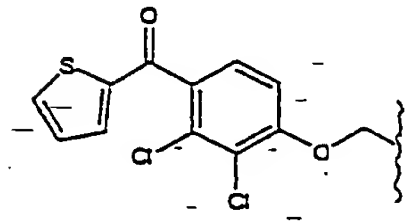


(V Ac5)

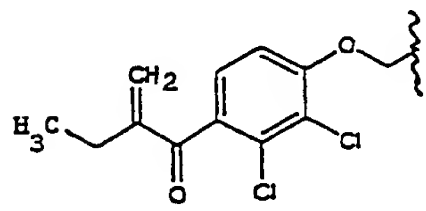
subgroup - V Ad) residues where [derivatives of diuretics when] t = 1 and R is as follows:



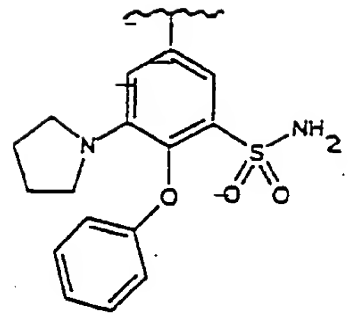
(V Ad1)



(V Ad2)

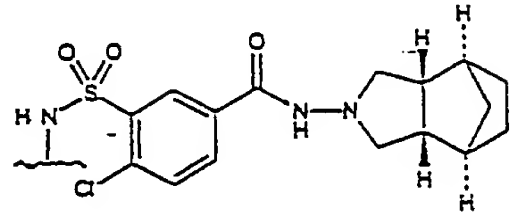


(V Ad3)

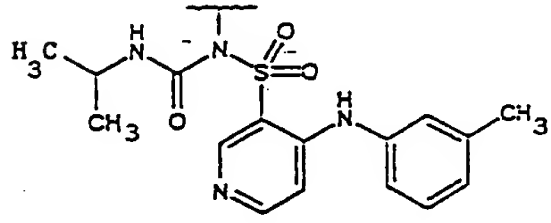


(V Ad4)

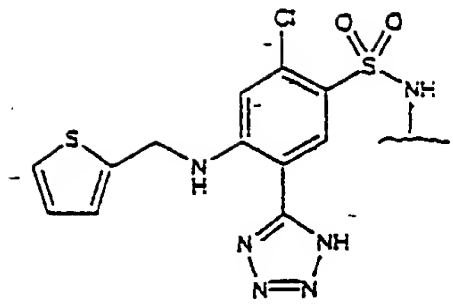
subgroup - V Ae) residues where [derivatives of diuretics] when t = 0 and R is as follows:



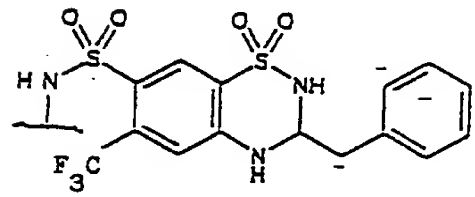
(V Ae1)



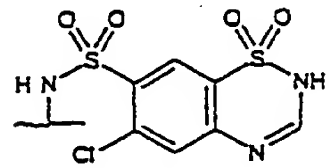
(V Ae2)



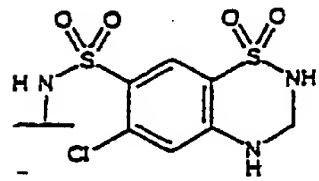
(V Ae3)



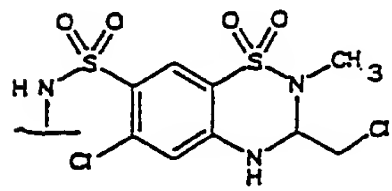
(V Ae4)



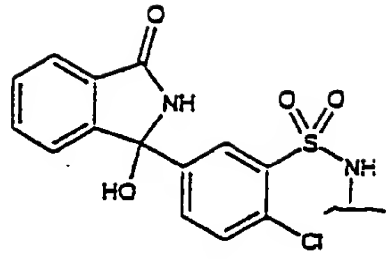
(V Ae5)



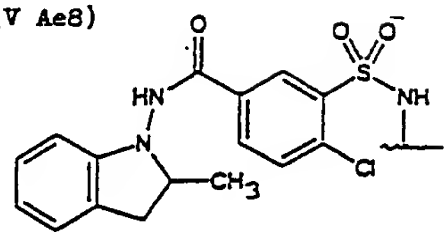
(V Ae6)



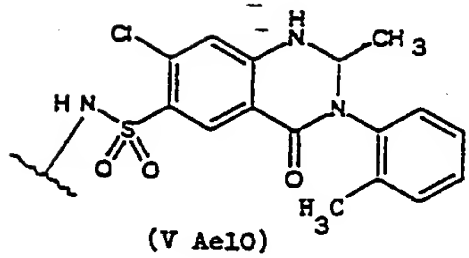
(V Ae7)



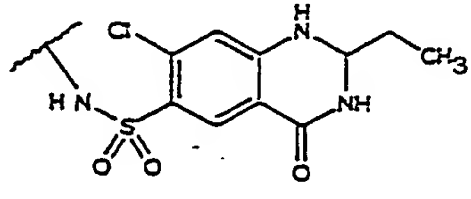
(V Ae8)



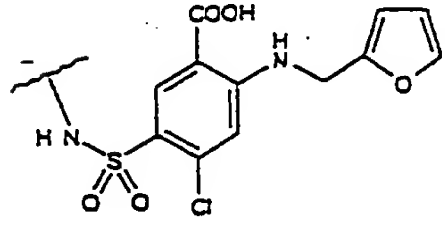
(V Ae9)



(V Ae10)



(V Ae11)



(V Ae12)

wherein [the meaning in group V A) is as follows:

- in compounds (V Aa1) the residue of enfenamic acid, 2 - ((phenylethyl) amino) benzoic acid[, has been shown];

- in compounds (V Aa2) the residue of flufenamic acid, 2 - ((3-(trifluoromethyl) phenyl) - amino) benzoic acid[, has been shown];

- in compounds (V Aa3) the residue of meclofenamic acid, 2 - ((2, 6-dichloro-3-methylphenyl) amino) benzoic acid[, has been shown];

- in compounds (V Aa4) the residue of mefanamic acid, 2 - ((2, 3-dimethylphenyl) amino) benzoic acid[, has been shown];

- in compounds (V Aa5) the residue of tolfenamic acid, 2 - ((3-chloro-2-methylphenyl) amino) benzoic acid, has been shown;

- in compounds (V Ab1) the residue of niflumic acid, 2 - ((3-(trifluoromethyl) phenyl) amino) - 3-pyridine carboxylic acid, has been shown;

-] in residue [compounds] (V Ac1), R_{vac1} is [attached to the oxygen atom in position 2 of the benzene ring of N-(4-nitrophenyl) methansulphonamide can be] phenyl or cycloexane[. When R_{vac1} is phenyl the residue is that of nimesulide;

- in compounds (V Ac2) the residue is[of] 3-formylamino-7-methylsulfonylamino-6-phenoxy-4H-1-bezopyran-4-one [has been shown];

-] in residue [compounds] (V Ac3), the atom X_4 is [that links the radical 2, 4-difluorothiophenyl to position 6 of the indanone ring of the residue 5-methanesulfonamido-1-indanone can be] sulfur or oxygen;

[- in compounds (V Ac4) the residue of celecoxib 4-(5-(4-methylphenyl) -3-(trifluoromethyl) pyrazol-1-yl) benzensulphonamide, has been shown;

- in compounds (V Ac4) the residue of celecoxib 4-(5-(4-methylphenyl) -3-(trifluoromethyl) pyrazol-1-yl) benzensulphonamide, has been shown;

- in compounds (V Ac5) the residue of 6 - (2-(3-ethyl- 2, 3-dihydro-thiazolyl) thio-5-methanesulphonamido-3H-isobenzonfuran-1-one has been shown.;

- in compounds (V Ad1) the residue of bumetanide 3-(Aminosulfonyl) -5-(butylamino) -4-phenoxybenzoic acid has been shown;

- in compounds (V Ad2) the residue of ticrynafen (2,3-Dichloro-4- (2-thienylcarbonyl) -phenoxy) acetic acid has been shown;

- in compounds (V Ad3) the residue of ethacrynic acid (2, 3-Dichloro-4-(2methylene-1-oxobutyl) phenoxy) acetic acid, has been shown;

- in compounds (V Ad4) the residue of piretanide 3-(Aminosulfonyl) -4-phenoxy-5-(1-pyrrolidinyl) benzoic acid has been shown;

- in compounds (V Ae1) the residue of tripamide (3aα, 4α, 7α, 7aα) -3-(Aminosulphonyl) -4-chloro-N-(octaidro-4, 7-metano-2H-isoindol-2-yl) benzamide has been shown.;

- in compounds (V Ae2) the residue of torsemide N- (((1-Methylethyl) amino) carbony1) 4- ((3-methylphenyl)amino) -3- pyrinesulfonamide has been shown;

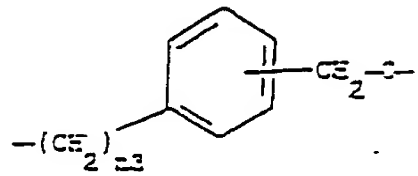
- in compounds (V Ae3) the residue of azosemide 2-Chloro-5- (1H-tetrazol-5-yl) -4-((2-thienylmethyl) amino) benzensulphonamide has been shown;

- in compounds (V Ae4) the residue of bendroflumethiazide 3,4-Dihydro-3-(phenyl-methyl) -6- (trifluoromethyl) -2H-1, 2, 4-benzothiadiazine-7-sulfonamide 1,1-dioxide has been shown;
- in compounds (V Ae5) the residue of chlorothiazide 6-Chloro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide has been shown;
- in compounds (V Ae6) the residue of hydrochlorotiazide 6-Chloro-3, 4-dihydro-2H-1,2,4-benzothiadiazine-7- sulfonamide 1,1-dioxide has been shown;
- in compounds (V Ae7) the residue of methylclothiazide (6-Chloro-3-(chloromethyl) -3, 4-dihydro-2-methyl-2H- 1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide has been shown;
- in compounds (V Ae8) the residue of chlorthalidone 2-Chloro-5- (2,3-dihydro-1-hydroxy-3-oxo-1H-isoindol-1-yl) benzensulfonamide has been shown;
- in compounds (V Ae9) the residue of Indapamide 3-(Aminosulfonyl) -4-chloro-N-(2,3-dihydro-2-methyl-1H- indol-l-yl) benzamide has been shown;
- in compounds (Vae10) the residue of metolazone 7-Chloro-1,2,3,4-tetrahydro-2-methyl -3- (2-methylphenyl) -4-oxo-6quinazolinesulfonamide has been shown;
- in compounds (V Ae11) the residue of quinetazone 7-Chloro-2-ethyl-1,2,3,4-tetrahydro-4-oxo-6-quinazoline-sulfonamide has been shown;
- in compounds (V Ae12) the residue of furosemide 5- (Aminosulfonyl) -4-chloro-2-((2-furanylmethyl) amino) benzoic acid has been shown.];

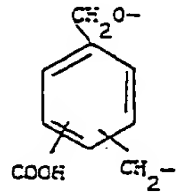
X_1 in formula A-X_1-NO_2 is a bivalent connecting bridge chosen from the following:

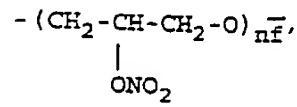
- YO

where Y is a linear or [whenever possible] branched C_1-C_{20} alkylene, [preferably having from 2 to 5 carbon atoms,] or an optionally substituted cycloalkylene having from 5 to 7 carbon atoms;

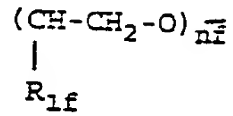


where n_3 is an integer from 0 to 3;





where nf' is an integer from 1 to 6, [preferably from 2 to 4];



where R_{1f} = H[,] or CH_3 and nf is an integer from 1 to 6[,] [preferably from 2 to 4].

2. (Twice Amended) [Use of the compounds] The method according to Claim 1, in which R is chosen from groups IV A) and V A).

5. (Amended) [Compounds or their compositions for use as medicaments from a grou V A) according to Claim 3] A method for the treatment of musculoskeletal disease of an inflammatory nature, gynaecological and obstetrical disease including early delivery, pre-eclampsia and dysmenorrhoea, cardiovascular disease including re-

stenosis, gastrointestinal tumors by administering compounds from group V A) according to Claim 3.